**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re the application of: Boussiotis et al.

Serial No.: 08/270,152

Filed: July 1, 1994

For: METHODS FOR MODULATING T CELL RESPONSES BY MANIPULATING A COMMON CYTOKINE RECEPTOR GAMMA CHAIN

Attorney Docket No.: RPI-022

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Group Art Unit: 1816

Examiner: Gambel, P.

Assistant Commissioner for Patents
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## APPEAL BRIEF

As set forth in the Notice of Appeal filed on June 24, 1997, and received by the U.S. Patent Office on June 24, 1997, Appellants hereby appeal the final decision of the Examiner in the above-identified application rejecting the subject matter of the pending claims. Appellants respectfully request that the Board of Patent Appeals and Interferences reverse the Examiner's rejection of the claimed subject matter.

## I. REAL PARTY IN INTEREST

The real party in interest in the above-identified application is Dana Farber Cancer Institute.

## II. RELATED APPEALS AND INTERFERENCES

No other appeals or interferences are known to Appellants, Appellants' legal representative or the assignees which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

## III. STATUS OF CLAIMS

Claims 48-101 were pending in this application. Claims 49, 51-54, 62-96 and 99-101 have been canceled without prejudice and claims 48, 50, 55-56, and 98 have been amended as described in the Amendment and Response to Final Office Action Pursuant to 37 C.F.R. §1.116, which is being filed on even date herewith. The amendment and/or cancellation of these claims reduces the number of issues for appeal. It is assumed that the Amendment and Response to Final Office Action will be entered for purpose of appeal and the claims argued herein will reflect this assumption. All of the pending claims are on appeal and are set forth in Appendix A of this Brief.

## IV. STATUS OF THE AMENDMENTS

An Amendment and Response to Final Office Action Pursuant to 37 C.F.R. §1.116 is being filed on even date herewith in response to the final Office Action (Paper No. 15) dated December 24, 1996 and the Advisory Action (Paper No. 18) dated July 16, 1997. A Notice of Appeal was filed separately by facsimile on June 24, 1997 and received by the U.S. Patent Office on June 24, 1997.

In the Amendment and Response to Final Office Action Pursuant to 37 C.F.R. §1.116, claims 49, 51-54, 62-96 and 99-101 have been canceled without prejudice and claims 48, 50, 55-56, and 98 have been amended.

The cancellation of claims 49, 51-54, 62-96 and 99-101 obviates the rejection of these claims under U.S.C. § 102. The amendments to claims 48 and 98 obviate the rejection of these claims and claims 50, 55, and 56, which depend therefrom, under U.S.C. § 102 and under U.S.C. § 112, second paragraph. Accordingly, the cancellation of claims 49, 51-54, 62-96 and 99-101 and the amendment of claims 48, 50, 55-56, and 98 reduces the number of issues for appeal.

It is assumed that the Amendment and Response to Final Office Action will be entered for purpose of appeal and the claims argued herein will reflect this assumption.

No other amendments after final have been filed. All other amendments have been entered.

## V. SUMMARY OF THE INVENTION

Appellants' invention pertains to a method for stimulating T cell responsiveness, e.g., in a T cell which has received a primary activation signal in the absence of a costimulatory signal.. The method includes contacting, e.g., *in vivo*, a T cell which expresses a cytokine receptor γ chain with an anti-γ chain antibody which binds to and transduces a signal via the γ chain such that T cell responsiveness is stimulated, as described at, for example, page 6, line 6 through page 13, line 2. The method can further include contacting the T cell, e.g., *in vitro* or *in vivo*, with an agent which stimulates a primary activation signal in the T cell or contacting the T cell with an agent, e.g., an antigen, which stimulates a costimulatory signal in the T cell, as described at, for example, page 20, lines 23-33. The antigen can be a pathogen or portion thereof selected from the group consisting of a virus, a bacteria, and a parasite, or a tumor antigen, as described at, for example, page 14, lines 33-38.

The invention finally pertains to a method for stimulating responsiveness in an anergic T cell. The method includes contacting said T cell with an anti-γ chain antibody which transduces a signal via the cytokine receptor γ chain such that T cell responsiveness is stimulated, as described at, for example, page 3, lines 26-29.

## VI. STATEMENT OF ISSUE PRESENTED FOR REVIEW

Appellants present the following issues for review:

I. Whether claims 48-61 and 97-101 are unpatentable under 35 U.S.C. § 112, first paragraph, as failing to be adequately described or enabled by the disclosure.

II. Whether claims 48, 56-61, 98 are indefinite for failing to distinctly claim the subject matter which Appellants regard as the invention under 35 U.S.C. § 112, second paragraph.

III. Whether claims 48-53, 55-58, 60-61, 97-100 are unpatentable under 35 U.S.C. § 102(e) as being anticipated by Plunkett et al. (U.S. Patent No. 5,382,427).

IV. Whether claims Claims 48-53, 55-61 and 97-100 are unpatentable under U.S.C. § 102(b) as being anticipated by Lee et al. (U.S. Patent No. 5,017,691).

V. Whether claims 48-53, 55-61 and 97-100 are unpatentable under U.S.C. § 102(a)(e) as being anticipated by Lynch et al. (U. S. Patent No. 5,229,115).

VI. Whether claims 48-53, 59, 61, 97-100 are unpatentable under U.S.C. § 102(e) as being anticipated by Grabstein et al. (U.S. Patent No.5, 474,769).

## VII. GROUPING OF CLAIMS

Claims 48 and 98 are Appellants' principal claims on appeal. Claim 48 is an independent genus claim drawn to a method for stimulating T cell responsiveness by contacting a T cell which expresses a cytokine receptor γ chain with an anti-γ chain antibody which binds to and transduces a signal via the γ chain such that T cell responsiveness is stimulated.

Claim 98 is an independent claim drawn to a method for stimulating responsiveness in an anergic T cell. The method includes contacting said T cell with an anti-γ chain antibody which transduces a signal via the cytokine receptor γ chain such that T cell responsiveness is stimulated.

Claims 50, 55-61 and 97 depend from claim 48. Claim 50 is directed to a method of claim 48 in which the T cell has received a primary activation signal in the absence of a costimulatory signal. Claim 55 is directed to a method of claim 48 in which the T cell is contacted *in vivo* with the anti-γ chain antibody. Claim 56 is directed to a method of claim 48 which further includes contacting the T cell with an agent which stimulates a primary activation signal in the T cell. Claim 57 is directed to a method of claim 56 which further includes contacting the T cell with an agent which stimulates a costimulatory signal in the T cell. Claim 58 is directed to a method of claim 56 in which the agent which stimulates a primary activation signal in the T cell is an antigen. Claim 59 is directed to a method of claim 58 in which the antigen is a pathogen or portion thereof selected from the group consisting of a virus, a bacteria, and a parasite. Claim 60 is directed to a method of claim 58 in which the antigen is a tumor antigen. Claim 61 is directed to a method of claim 58 in which the T cell is contacted with the antigen *in vivo*. Claim 97 is directed to a method of claim 50 in which the T cell is contacted with the agent *in vitro*.

The rejected claims do not stand or fall together for the reasons set forth below.

## VIII. ARGUMENTS

**Rejection of Claims 48-61 and 97-101 Under 35 U.S.C. § 112, First Paragraph**

Claims 48-61 and 97-101 are rejected under 35 U.S.C. §112, first paragraph, based on the Examiner's assertion that "there is insufficient objective evidence to support the breadth and the predictability of modulating/inhibiting responsiveness of normal or primed T cells either ex-vivo as well as in-vivo." In particular, the Examiner argues that "there is insufficient objective evidence to support the breadth and the predictability of modulating/inhibiting responsiveness of

normal or primed T cells either ex-vivo as well as in-vivo." Moreover, the Examiner states that "the issue involved is whether or not the evidence of record, based on in-vitro studies, is generally recognized by those of ordinary skill in the art, as being ***reasonably predictive of success in the practical in-vitro and in-vivo therapeutic methods encompassed by the instant claims***." The Examiner further states that the issue is "whether Appellants specification provides insufficient information or nexus which enables any person skilled in the art to use the full scope of the broadly claimed therapeutic methods of modulating or inhibiting unresponsiveness in T cells."

Appellants respectfully submit that this rejection does not apply to the claims as amended. First, claims 49, 51-54, 62-96 and 99-101 have been cancelled and, thus, as applied to these claims the rejection is obviated. Second, as amended, independent claims 48 and 98 are drawn to a method for stimulating T cell responsiveness by contacting a T cell which expresses a cytokine receptor γ chain with an anti-γ chain antibody which binds to and transduces a signal via the γ chain such that T cell responsiveness is stimulated. All of the remaining claims depend from claim 48. As the amended claims are directed to the use of an anti-γ chain antibody to stimulate T cell responsiveness, Appellants respectfully submit that the above-quoted rejection under 35 U.S.C. §112, first paragraph is obviated.

However, Appellants wish to make the following remarks in support of their position that the specification fully enables the claimed invention. The above quoted rejection of claims 48, 50, 55-61 and 97-98 is respectfully traversed on the grounds that the present specification does provide adequate guidance which would enable the ordinarily skilled artisan to make and use the claimed invention. First, it is respectfully submitted that the relevant question is whether the specification "adequately teaches one of ordinary skill in the art how to make or use ***the claimed invention***." The proper standard for judging enablement of claims involving an asserted therapeutic effect is whether the Appellants disclosure provides sufficient guidance and data which would lead one of ordinary skill in the art to ***reasonably*** believe the asserted utility or effect (*In re Brana* 51 F.3d 1560; 34 U.S.P.Q.2D 1437 (CAFC, decided March 30, 1995). The

Court of Appeals for the Federal Circuit specifically held that if a patent disclosure presents a working description of an invention and data to support its utility which could be reasonably applied to *in vivo* systems, then further evidence should ***not*** be required to satisfy the enablement requirement of section 112, first paragraph, ***unless there is reason to doubt the objective truth*** of the asserted utility. It is Appellants position that the disclosure fully satisfies this enablement standard.

For example, Appellants specification teaches recombinant expression vectors for expressing proteins or peptides (i.e., an ***anti-γ chain antibody***) in cells (e.g., recombinant viral vectors), and nucleic acid delivery mechanisms suitable for gene therapy *in vitro* or *in vivo* at, for example, page 12, lines 26-35. Moreover, at page 18, line 16 through page 20, line 19, methods for administering agents, e.g., anti-γ chain antibodies, to subjects to stimulate T cell responses, are described. Further, Appellants disclosure provides specific, working examples demonstrating that agents within the scope of Appellants claim prevented the induction of T cell anergy in a human alloantigen specific T cell clonal model system (see Examples 1 and 2 on pages 21 and 23, respectively). The data presented in the specification is more than reasonably indicative of *in vivo* efficacy as asserted and claimed by Appellants. Human T cells and the cell lines described in the disclosure are routinely used to illustrate immune system responses *in vitro* and are art-accepted models of *in vivo* therapeutic efficacy.

In view of the above, the ordinarily skilled artisan would not have been required to use "undue experimentation" to practice the claimed invention as alleged by the Examiner. Thus, the ordinarily skilled artisan, following a careful reading of the above-described teachings from Appellants' specification can make and use the claimed invention. Accordingly, it is respectfully submitted that claims 48, 50, 55-61 and 97-98 are fully enabled by the disclosure.

**Rejection of Claims 48, 56-61 and 98 Under U.S.C. §112 Second Paragraph**

Claims 48, 56-61, 98 are rejected under U.S.C. §112 second paragraph as being indefinite and ambiguous in the recitation of the phrases "modulating T cell responsiveness" and "such that

the T cell responsiveness is modulated" in the absence of a clear positive or negative effect. In particular, the Examiner states that the term "modulation" is not appropriate "because modulation can occur both in positive and negative directions and applicant elected methods of stimulating T cells."

Appellants respectfully submit that the above rejection does not apply to the claims as amended. In particular, claims 48 and 98 have been amended as suggested by the Examiner to recite "[a] method for ***stimulating*** T cell responsiveness." Accordingly, in view of the cancellation and amendments to these claims the rejection under 35 U.S.C. 112, second paragraph, has been obviated.

**Rejection of claims 48-53, 55-58, 60-61, 97-100 Under U.S.C. § 102**

Claims 48-53, 55-58, 60-61, 97-100 stand rejected under U.S.C. § 102(e) as being anticipated by Plunkett et al. (U.S. Patent No. 5,382,427). Claims 48-53, 55-61 and 97-100 stand rejected under U.S.C. § 102(b) as being anticipated by Lee et al. (U.S. Patent No. 5,017,691). Claims 48-53, 55-61 and 97-100 stand rejected under U.S.C. § 102(a)(e) as being anticipated by Lynch et al. (U. S. Patent No. 5,229,115). Claims 48-53, 59, 61, 97-100 stand rejected under U.S.C. § 102(e) as being anticipated by Grabstein et al. (U.S. Patent No.5, 474,769). The Examiner asserts that the cytokines and methods of use taught in each of the aforementioned references meet the limitations of the presently claimed methods, and that the functional limitations recited in the present claims "would be addressed by the inherent properties of the referenced methods."

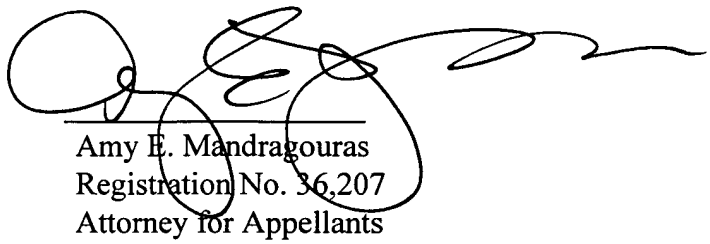
Appellants respectfully submit that the above rejection does not apply to the claims as amended. First claims 49, 51-54, 62-96 and 99-101 have been cancelled and, thus, as applied to these claims the rejection is obviated. Second, independent claims 48 and 98 have been amended to incorporate the limitations of claims 54 and 101 which were indicated by the Examiner in Paper No. 15, page 7, paragraph 14, to be free of the prior art. Accordingly, Appellants submit that claims 48 and 98, as well as claims 50, 55-61, 97 and 98 which depend from claim 48, are

free of the prior art. Therefore, Appellants respectfully submit that claims 48, 50, 55-61 and 97-98 are patentable in view of the cited art.

## VII. CONCLUSION

Appellants submit that pending claims 48, 50, 55-61 and 97-98 are patentable and it is respectfully requested that the Board reverse the final rejection of the subject matter of these claims for the reasons given above.

Respectfully submitted,



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## APPENDIX A

48. A method for stimulating T cell responsiveness, comprising contacting a T cell which expresses a cytokine receptor γ chain with an anti-γ chain antibody which binds to and transduces a signal via the γ chain such that T cell responsiveness is stimulated.

50. The method of claim 48, wherein the T cell has received a primary activation signal in the absence of a costimulatory signal.

55. The method of claim 48, wherein the T cell is contacted *in vivo* with the anti-γ chain antibody.

56. The method of claim 48, further comprising contacting the T cell with an agent which stimulates a primary activation signal in the T cell.

57. The method of claim 56, further comprising contacting the T cell with an agent which stimulates a costimulatory signal in the T cell.

58. The method of claim 56, wherein the agent which stimulates a primary activation signal in the T cell is an antigen.

59. The method of claim 58, wherein the antigen is a pathogen or portion thereof selected from the group consisting of a virus, a bacteria, and a parasite

60. The method of claim 58, wherein the antigen is a tumor antigen.

61. The method of claim 58, wherein the T cell is contacted with the antigen *in vivo*.

97. The method of claim 50, wherein the T cell is contacted with the agent *in vitro*.

98. A method for stimulating responsiveness in an anergic T cell, comprising contacting said T cell with an anti-γ chain antibody which transduces a signal via the cytokine receptor γ chain such that T cell responsiveness is stimulated.